AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 124, No. 4
Printed in U.S.A.

METHYLXANTHINES AND BENIGN BREAST DISEASE[1]

CATHERINE SCHAIRER,[2] LOUISE A. BRINTON, AND ROBERT N. HOOVER

Schairer, C. (Environmental Epidemiology Branch, NCI, NIH, Bethesda, MD 20892), L. A. Brinton, and R. N. Hoover. Methylxanthines and benign breast disease. *Am J Epidemiol* 1986;124:603–11.

The relation between methylxanthine consumption and biopsied benign breast disease was investigated by using data from a case-control study which included 1,569 cases and 1,846 controls identified between 1973 and 1980 through a nationwide screening program. There was no evidence of an association between methylxanthine consumption and benign breast disease in the total study population. When histologic types of benign breast disease were examined, there were no trends in risk according to methylxanthine consumption among the 813 cases with fibrocystic disease, the 508 cases for whom detailed pathology data were not available, the 172 cases with benign neoplasms, or the 156 cases with other benign conditions. When cases with fibrocystic disease were examined according to presence of atypia, hyperplasia, sclerosing adenosis, or cysts, there was, again, no association between methylxanthine consumption and risk of disease. In addition, no relation was found between methylxanthine consumption and menstrual breast tenderness among premenopausal women with fibrocystic disease or unknown conditions.

breast neoplasms; coffee; fibrocystic disease of breast

Reports linking abstention from methylxanthines (caffeine, theophylline, and theobromine) with the resolution of symptoms of fibrocystic breast disease (1, 2) have sparked considerable interest in the role of methylxanthines in both the etiology and treatment of benign breast disease. Although two case-control studies (3, 4) have found a positive association between methylxanthine consumption and fibrocystic breast disease, suggesting an etiologic relation, several other case-control studies have shown no association with benign breast disease in general (5) or with fibrocystic disease (6, 7). Results concerning the role of methylxanthines in the treatment of benign breast disease have also been conflicting. One uncontrolled trial (8) found improvement in breast symptoms related to fibrocystic disease after abstention from methylxanthines, whereas a controlled randomized trial (9) and a study

Received for publication December 13, 1985, and in final form April 7, 1986.

Abbreviation: cyclic AMP, adenosine 3′,5′-cyclic phosphate.

[1] Environmental Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.

[2] Reprint requests to Catherine Schairer, Environmental Epidemiology Branch, National Cancer Institute, National Institutes of Health, Landow Building, Room 3C-06, Bethesda, MD 20892.

The authors thank Dr. George Foradori, Dr. Oswald DeLisser, Najma Khalid, and Bernadine Hawes of the Data Management and Analysis Center and the directors and coordinators at the 28 participating centers of the Breast Cancer Detection Demonstration Project for identifying study subjects and encouraging their cooperation; Shirley Blumberg, Dr. Joan Cwi, Leslye Goren, Diane Monheit, and Helen Price of Survey Research Associates for supervising the conducting of the interviews; Dr. Ann Dudgeon, Debbie Kahn, and Linda Lesher of ORI, Inc. for data editing and computer assistance; Kimberly Young for help with the manuscript; and Dr. Richard Costlow of the Division of Cancer Prevention and Control of the National Cancer Institute for his support of this study.

evaluating breast nodularity over a six-month period during which methylxanthine consumption was fairly constant (10) failed to substantiate claims that methylxanthine consumption is related to resolution of symptoms of fibrocystic breast disease.

To evaluate further the relation between methylxanthines and benign breast disease, we examined data from a case-control study which gathered detailed information on consumption of methylxanthine-containing beverages.

Materials and Methods

Study subjects were participants in the Breast Cancer Detection Demonstration Project, a five-year breast cancer screening program sponsored jointly by the National Cancer Institute and the American Cancer Society. The program, begun in 1973, provided up to five annual breast examinations, each of which consisted of a clinical examination in conjunction with mammography and thermography, to more than 280,000 women in 29 centers throughout the United States.

The methodology for an earlier case-control study based on screening participants has been described in a previous publication (11). In a continuation of this study, a number of questions on the consumption of beverages containing methylxanthines were added to the questionnaire. The cases in this analysis were drawn from screening participants who underwent surgical evaluation which indicated benign rather than malignant breast disease. The controls were selected from women who were neither recommended for nor underwent surgical evaluation during screening participation. Because this study was also designed to look at risk factors for breast cancer, both the benign breast disease cases and the controls in this analysis were selected to be similar to breast cancer cases in regard to screening center, age (same five-year age group), race (white, black, Asian, or other), time of entry into the screening program (within the same six-month period), and length of participation in the program.

Home interviews lasting approximately one hour were obtained for 2,040 (86 per cent) cases and 2,125 (90 per cent) controls. Refusal (7 per cent of the cases vs. 6 per cent of the controls) was the major reason for nonresponse of study subjects. In addition, small numbers of interviews were not completed due to death, illness, and miscellaneous reasons. Using data gathered at entry into the screening program, we determined that women who were not interviewed were older, had lower family incomes, and were more often nonwhite than were women who were interviewed. Interviewed and noninterviewed women did not differ significantly, however, according to history of benign breast surgery prior to the screening program.

Study subjects who reported having a breast malignancy which was detected before entry into the screening program (44 cases and 26 controls) were eliminated from all analyses, as were nonwhite women, who comprised 9.2 per cent of the study subjects.

In addition to information on risk factors for both breast cancer and benign breast disease, extensive information was gathered during the interviews on both seasonal and year-round consumption of the following beverages which contain methylxanthines: brewed coffee with caffeine (approximately 128 mg caffeine per 150 ml cup), instant coffee with caffeine (66 mg caffeine per 150 ml cup), decaffeinated coffee (3 mg caffeine per 150 ml cup), hot nonherbal tea (38 mg caffeine and 3 mg theobromine per 150 ml cup), hot cocoa (4 mg caffeine and 65 mg theobromine per 150 ml cup), iced tea (47 mg caffeine per 8 oz glass), chocolate milk (5 mg caffeine and 58 mg theobromine per 240 ml glass), cola soft drinks (24 mg caffeine per 240 ml glass), and diet cola drinks (24 mg caffeine per 240 ml glass) (12, 13). Subjects were asked how many servings of these beverages they drank per week during three age periods (<30, 30–49, ≥ 50 years) until their ages at entry into the screening program.

For purposes of analysis, we calculated age-specific estimates as well as overall weighted averages of total methylxanthine consumption, caffeine consumption, and daily servings of each beverage. Because results for total methylxanthine consumption were similar to those for consumption of caffeine alone, we present results primarily for total methylxanthine consumption. We also focus on daily methylxanthine consumption averaged over the three age periods, but present results specific for each age period as well. A total of 53 cases and 47 controls had unknown reported frequency for at least one beverage and were excluded from all analyses.

Information on histology obtained from hospital pathology reports was available for the cases. Although these reports came from a number of hospitals, they were reviewed and then recoded onto standardized forms by project pathologists associated with each center. Cases with no pathology reports (5 cases), bilateral pathology reports (179 cases), or conflicting reports on the same breast (10 cases) were excluded from all analyses after we determined by comparison with control subjects that there was no association between methylxanthine consumption and breast disease among these women. Of the remaining 1,569 cases, 733 had fibrocystic disease but no benign neoplasms (benign neoplasms consisted primarily of fibroadenoma or unspecified benign neoplasms), 80 had both fibrocystic disease and benign neoplasms, 92 had benign neoplasms but no fibrocystic disease, 156 had benign conditions other than fibrocystic disease or benign neoplasms (primarily calcification or unspecified nonneoplastic lesions), and 508 had unknown conditions due to incomplete pathology reports (239 of these had aspirations only and 269 had biopsies).

For the final analysis, the 80 cases with fibrocystic disease and benign neoplasms were included both with the 733 cases who had only fibrocystic disease and with the 92 cases who had benign neoplasms without accompanying fibrocystic disease. This resulted in a total of 813 cases with fibrocystic disease and 172 cases with benign neoplasms. The 813 cases with fibrocystic disease were further classified into the following categories (determined hierarchically): ductal (74 cases) or lobular (19 cases) hyperplasia with atypia, ductal or lobular hyperplasia without atypia (475 cases), sclerosing adenosis (58 cases), or epithelial cysts (187 cases).

To evaluate the effect of methylxanthine consumption on risk of disease, odds ratios (OR) and 95 per cent confidence intervals (CI) were derived (14). An extension of the Mantel-Haenszel procedure (15) with one-tailed p values was used to test for the statistical significance of trends. Matched analyses were also done, but because results were similar to those from the unmatched analyses, only unmatched estimates are presented.

Results

Table 1 presents the age distributions and mean ages of the controls and cases classified by type of benign breast disease. Cases with fibrocystic disease and benign neoplasms were similar to the controls with regard to age, whereas cases with other conditions were on average slightly older and cases with unknown conditions were slightly younger than the controls.

A higher percentage of cases than controls experienced breast tenderness during menstruation, had a history of breast biopsies before entering the screening program, had a history of breast cancer in a first-degree relative, or were long-term users of menopausal estrogens. Controls, on the other hand, were more likely to have been oral contraceptive users, were more likely to have been menopausal, had attained more education, and were heavier as measured by Quetelet index. However, adjustment for these factors or for age at diagnosis did not appreciably alter results, so unadjusted estimates are presented.

Average daily methylxanthine intake was 356 mg for cases and 353 mg for controls. Over 90 per cent of both cases and controls

TABLE 1

Age distributions of controls and cases according to benign breast disease type, Breast Cancer Detection Demonstration Project, 1973–1980

Age (years)	Controls (n = 1,846)		Fibrocystic disease (n = 813)		Unknown (n = 508)		Benign neoplasms (n = 172)		Other (n = 156)	
	No.	%	No.	%	No.	%	No.	%	No.	%
<40	85	5	29	4	22	4	13	8	6	4
40–44	193	10	80	10	74	15	18	10	13	8
45–49	315	17	125	15	96	19	24	14	15	10
50–54	354	19	159	20	102	20	24	14	26	17
55–59	354	19	146	18	98	19	38	22	27	17
>60	545	30	274	34	116	23	55	32	69	44
Mean age (years)	54.5		55.5		53		55.2		57.5	

TABLE 2

Odds ratios (OR) associated with methylxanthine consumption among all cases and controls, Breast Cancer Detection Demonstration Project, 1973–1980

Methylxanthines (mg/day)	Controls (n = 1,846)	Cases (n = 1,569)	OR	95% confidence interval
≤125	294	255	1.0*	
126–250	462	399	1.0	0.8–1.2
251–500	678	557	1.0	0.8–1.2
501–750	274	227	1.0	0.7–1.2
>750	138	131	1.1	0.8–1.5
Mantel trend test, p			0.47	

* Reference category is consumers of ≤125 mg of methylxanthines per day.

had ever consumed either brewed or instant coffee, while approximately 88 per cent had ever consumed hot or iced tea, and 71 per cent had ever consumed cola soft drinks or diet cola drinks. Only 54 per cent of both cases and controls, on the other hand, reported ever having consumed hot cocoa or chocolate milk. Because only three cases and nine controls reported no consumption of beverages containing methylxanthines, consumers of less than 126 mg per day (the equivalent of approximately one cup of brewed coffee with caffeine) were used as the reference group when calculating odds ratios.

For the total study population (table 2), there was no evidence of an association between methylxanthine consumption and benign breast disease (trend test, $p = 0.47$). Odds ratios associated with average daily methylxanthine consumption according to type of benign breast disease are presented in table 3. Among cases with fibrocystic disease, there was no evidence of an association between methylxanthine consumption and risk of disease, with consumers of more than 750 mg per day (the equivalent of approximately six or more cups of brewed coffee with caffeine) having an odds ratio of 0.9 compared with light consumers. Similarly, there was no evidence of increased risk among cases with unknown pathologic conditions. When those with unknown conditions who had had an aspiration only (most likely indicating cystic disease) were examined separately from those who had had a biopsy, there was again no relation between methylxanthine consumption and disease. Among cases with benign neoplasms, there was also no evidence of increased risk associated with methylxanthine consumption. Although

odds ratios were elevated among cases with other conditions, there did not appear to be a dose-response relation ($p = 0.18$).

Results were similar for all case groups when exposure was limited to milligrams of caffeine, rather than to methylxanthines. In addition, no statistically significant associations were evident between average daily servings of brewed coffee with caffeine and risk of disease for any of the case groups.

When cases with fibrocystic disease were examined by presence of selected histopathologic breast changes (table 4), there again was no evidence of an association between methylxanthine consumption and risk of disease. Although numbers were too small for a meaningful analysis of ductal versus lobular atypia, there was no evidence of excess risk in either group. In addition, no associations were evident when consumption of caffeine alone or average daily servings of brewed coffee with caffeine were examined.

For all case groups, odds ratios associated with methylxanthine consumption did not vary significantly according to age at diagnosis, number of previous breast biopsies, smoking status, use of oral contraceptives, use of menopausal estrogens, menopausal status, weight, Quetelet index, age at first livebirth, presence of menstrual breast tenderness, family history of breast cancer, income, or education.

Although consumption was, on average, highest between ages 30 and 49 years for both cases and controls, too few women reported substantial enough changes in consumption between age periods to allow effective evaluation of high consumption during one specific age period but not others. We were able, however, to examine risk associated with past and recent consumption, i.e., consumption prior to and at the time of entry into the screening program. Results for controls and cases with fibrocystic disease and unknown pathologic conditions who entered the screening program

TABLE 3

Odds ratios (OR) associated with methylxanthine consumption according to type of benign breast disease, Breast Cancer Detection Demonstration Project, 1973–1980

Methylxanthines (mg/day)	No. of controls (n = 1,846)	Fibrocystic disease (n = 813)		Unknown (n = 508)		Benign neoplasms (n = 172)		Other (n = 156)	
		No.	OR	No.	OR	No.	OR	No.	OR
≤125	294	143	1.0*	84	1.0*	28	1.0*	18	1.0*
126–250	462	212	0.9	123	0.9	42	1.0	41	1.4
251–500	678	272	0.8	192	1.0	62	1.0	63	1.5
501–750	274	124	0.9	65	0.8	27	1.0	20	1.2
>750	138	62	0.9	44	1.1	13	1.0	14	1.7

* Reference category is consumers of ≤125 mg of methylxanthines per day.

TABLE 4

Odds ratios (OR) associated with methylxanthine consumption among controls and cases with fibrocystic breast disease: cases subdivided by the presence of selected histopathologic breast changes, Breast Cancer Detection Demonstration Project, 1973–1980

Methylxanthines (mg/day)	No. of controls (n = 1,846)	Atypia (n = 93)		Hyperplasia (n = 475)		Sclerosing adenosis (n = 58)		Cysts (n = 187)	
		No.	OR	No.	OR	No.	OR	No.	OR
≤125	294	14	1.0*	82	1.0*	12	1.0*	35	1.0*
126–250	462	31	1.4	129	1.0	12	0.6	40	0.7
251–500	678	29	0.9	147	0.8	23	0.8	73	0.9
>500	412	19	1.0	117	1.0	11	0.7	39	0.8

* Reference category is consumers of ≤125 mg of methylxanthines per day.

after age 49 years are presented in table 5. For both case groups, there was little evidence of a positive association between risk of disease and methylxanthine consumption either before age 30 years, between ages 30 and 49 years, or at or after age 50 years. The lack of a significant effect was also evident under various assumptions about induction time, which we examined by looking at the age-specific estimates of consumption according to age at diagnosis. In addition, no substantial variations in risk were seen according to recency of use or to induction time among women who entered the screening program before age 50 years.

In view of reports that abstention from methylxanthines alleviates breast symptoms generally associated with fibrocystic disease (1, 2), we examined the relation between methylxanthine consumption and menstrual breast tenderness. Results were limited to premenopausal women, both to increase the accuracy of recall of breast tenderness and to be consistent with a previous report (3). Although premenopausal cases with fibrocystic disease or unknown conditions experienced menstrual breast tenderness more frequently than did controls (fibrocystic disease: OR = 1.4, 95 per cent CI = 1.0–1.9; unknown conditions: OR = 1.3, 95 per cent CI = 0.9–1.8), there appeared to be no relation between methylxanthine consumption and breast tenderness in either group (table 6). Among the controls, however, odds ratios rose to 2.3 among women who consumed between 501 and 750 mg per day, but fell to 1.1 among the heaviest consumers (p value for trend = 0.06). Results were similar when analyses were limited to controls who reported never having had a biopsy before entry into the screening program.

Discussion

Minton et al. hypothesized that methylxanthines, either by inhibiting phosphodiesterase breakdown of adenosine 3′,5′-cyclic phosphate (cyclic AMP) (1, 2), a cell nucleotide that plays a key role in the action of a number of hormones, or by increasing catecholamine release (16), may increase cellular levels of cyclic AMP sufficiently to contribute to the excessive cellular proliferation characteristic of fibrocystic disease. While there is considerable evidence that methylxanthines inhibit phosphodiesterase breakdown of cyclic AMP and that cyclic AMP stimulates events leading to cell proliferation (17), the

TABLE 5

Odds ratios (OR) associated with methylxanthine consumption during three age periods for cases and controls who entered the screening program after age 49 years, Breast Cancer Detection Demonstration Project, 1973–1980

Methylxanthines (mg/day)	Age (years)					
	<30		30–49		≥50	
	No.	OR	No.	OR	No.	OR
Fibrocystic disease						
≤125	133	1.0*	91	1.0*	172	1.0*
126–250	155	1.1	145	1.0	112	0.7
251–500	154	0.8	178	0.8	149	0.8
501–750	60	1.0	79	0.9	74	0.9
>750	43	1.4	52	1.0	38	0.9
Unknown						
≤125	71	1.0*	44	1.0*	89	1.0*
126–250	68	0.9	79	1.2	65	0.8
251–500	96	0.9	102	1.0	96	0.9
501–750	35	1.1	45	1.0	30	0.7
>750	21	1.3	21	0.8	11	0.5

* Reference category is consumers of ≤125 mg of methylxanthines per day.

TABLE 6

Odds ratios (OR) associated with methylxanthine consumption as a risk factor for menstrual breast tenderness among premenopausal controls and cases with fibrocystic disease and unknown conditions, Breast Cancer Detection Demonstration Project, 1973–1980

Methylxanthines (mg/day)	Menstrual breast tenderness		OR
	Yes	No	
Fibrocystic disease			
≤125	23	22	1.0*
126–250	29	23	1.2
251–500	32	45	0.7
501–750	26	17	1.5
>750	10	10	1.0
Unknown conditions			
≤125	12	14	1.0*
126–250	24	17	1.6
251–500	36	36	1.2
501–750	9	18	0.6
>750	9	13	0.8
Controls			
≤125	26	54	1.0*
126–250	51	78	1.4
251–500	87	105	1.7
501–750	42	38	2.3
>750	18	33	1.1
Mantel trend test, *p*			0.06

* Reference category is consumers of ≤125 mg of methylxanthines per day.

relation between methylxanthine consumption and cellular levels of cyclic AMP remains unclear. Certain investigators have found, for instance, that cells treated with caffeine do not accumulate cyclic AMP (18). In fact, they report that levels of caffeine normally consumed by humans are far below levels demonstrated to raise cyclic AMP levels. In addition, while there is evidence that acute ingestion of caffeine can increase catecholamine levels, chronic ingestion appears to have little or no effect (19).

Overall, the results of this study do not support the hypothesis that methylxanthine consumption is related to either the etiology or symptomatology of fibrocystic breast disease. Among cases with fibrocystic disease, there was no evidence of increased risk with increased average daily consumption of methylxanthines. In addition, no associations were found for either past or recent consumption or for any subtypes of fibrocystic disease. Among cases with unknown benign conditions, many of whom probably had cystic disease, there was also no association between methylxanthine consumption and risk of disease. We also found no consistent relation between methylxanthine consumption and risk for benign neoplasms or other conditions, conditions not specifically hypothesized to be linked to methylxanthine consumption. When the analysis was confined to consumption of caffeine alone, there was also no increased risk of disease.

Our findings are consistent with those of several other case-control studies (5–7) which have examined the relation between methylxanthines and the etiology of benign breast disease, one of which also examined risk according to histologic type of benign breast disease (5). Two case-control studies (3, 4) have, however, found a positive association between coffee consumption and fibrocystic disease. A hospital-based study of cases with biopsy-confirmed fibrocystic disease found a 2.3-fold increase in the odds among women who drank over 500 mg of caffeine per day (3). Another study based on cases with histologically confirmed fibrocystic disease found odds ratios associated with consumption of three or more cups of coffee per day of 3.7 when outpatient controls were the comparison group and 6.4 when hospital controls were utilized (4). The fact that these were hospital-based studies and that ours was not may explain the discrepancies in our results, although both studies addressed issues which have been raised concerning the use of hospital controls in studying the effects of coffee on disease (20, 21).

Although we were not able to evaluate directly the effects of methylxanthine abstention on breast symptoms associated with fibrocystic disease, we did not find that methylxanthine consumption was related to menstrual breast tenderness among premenopausal cases with fibrocystic disease or unknown conditions. Boyle et al.

(3) also found no association between methylxanthine consumption and premenstrual breast symptomatology among cases with fibrocystic disease. In addition, a randomized trial of the effects of a caffeine-free diet on benign breast disease (9), as well as a prospective study of fibrocystic disease and caffeine consumption (10), provide little evidence that methylxanthine consumption is associated with the resolution of symptoms of fibrocystic disease. These results contrast, however, with those from studies (1, 2, 8) that have reported resolution of breast symptoms in some women who abstained from methylxanthines. Some methodologic concerns have been raised (22), however, concerning reports by Minton et al. (1, 2), while the findings of Brooks et al. (8) are questionable due to the absence of a comparison group of women who did not abstain from caffeine.

In evaluating the results of this study, several methodologic issues require consideration. Because the purpose of the Breast Cancer Detection Demonstration Project was to screen for breast cancer, women in the screening program were only biopsied if they were suspected of having malignant rather than benign breast disease. Thus, some of the controls in this study may have had clinical benign breast disease. In addition, some of the controls had a history of biopsied benign breast disease before entering the screening program. Elimination of these women from the analyses did not, however, alter results. The benign cases in this study were also chosen to be similar to breast cancer cases with regard to age. Because breast cancer has an older age distribution than does benign breast disease (23), this resulted in an older and somewhat unrepresentative series of benign cases. We did, however, examine results specific to age at diagnosis and did not find any excess risk among the younger cases. Questionnaires were also administered in 1982 and 1983, well after articles hypothesizing the relation between methylxanthines and fibrocystic disease were first published in 1979 (1, 2). Although the questionnaires elicited information on methylxanthine consumption only until the subjects' ages at entry into the screening program (corresponding to the years 1973–1975), it is possible that some misclassification of methylxanthine consumption resulted from the subsequent publicity. Although systematic bias could have masked a substantial association, it is unlikely that random misclassification could have done so (24). In addition, it is unlikely that misclassification bias could totally account for the overall lack of association found in this study, particularly given that we found no evidence of increased risk with either past or recent consumption. Finally, information was not available on consumption of chocolate-containing foods and candies or of caffeine-containing pills such as analgesics, common cold remedies, allergy and weight control medications, diuretics, and stimulants.

In summary, our findings indicate that there is no association between methylxanthine consumption and biopsied benign breast disease. Our results are consistent with those of several epidemiologic studies undertaken to address this issue as well as with results from laboratory studies which have measured physiologic response to caffeine consumption.

References

1. Minton JP, Foecking MK, Webster DJ, et al. Caffeine, cyclic nucleotides, and breast disease. Surgery 1979;86:105–9.
2. Minton JP, Foecking MK, Webster DJ, et al. Response of fibrocystic disease to caffeine withdrawal and correlation of cyclic nucleotides with breast disease. Am J Obstet Gynecol 1979; 135:157–8.
3. Boyle CA, Berkowitz GS, LiVolsi VA, et al. Caffeine consumption and fibrocystic breast disease: a case-control epidemiologic study. JNCI 1984;72:1015–19.
4. La Vecchia C, Franceschi S, Parazzini F, et al. Benign breast disease and consumption of beverages containing methylxanthines. JNCI 1985; 74:995–1000.
5. Lubin F, Ron E, Wax Y, et al. A case-control study of caffeine and methylxanthines in benign breast disease. JAMA 1985;253:2388–92.
6. Lawson DH, Jick H, Rothman KJ. Coffee and tea consumption and breast disease. Surgery 1981;90:801–3.

7. Marshall J, Graham S, Swanson M. Caffeine consumption and benign breast disease: a case-control comparison. Am J Public Health 1982;72:610–12.
8. Brooks PG, Gart S, Heldfond AJ, et al. Measuring the effect of caffeine restriction on fibrocystic breast disease: the role of graphic stress telethermometry as an objective monitor of disease. J Reprod Med 1981;26:279–82.
9. Ernster VL, Mason L, Goodson WH, et al. Effects of caffeine-free diet on benign breast disease: a randomized trial. Surgery 1982;91:263–7.
10. Heyden S, Muhlbaier LH. Prospective study of "fibrocystic breast disease" and caffeine consumption. Surgery 1984;96:479–83.
11. Brinton LA, Hoover R, Fraumeni JF Jr. Epidemiology of minimal breast cancer. JAMA 1983;249:483–7.
12. Bunker ML, McWilliams M. Caffeine content of common beverages. J Am Diet Assn 1979;74:28–32.
13. Zoumas BL, Kreiser WR, Martin RA. Theobromine and caffeine content of chocolate products. J Food Sci 1980;45:314–16.
14. Gart JJ. Point and interval estimation of the common odds ratio in the combination of 2 × 2 tables with fixed marginals. Biometrika 1970;57:471–5.
15. Mantel N. Chi-square tests with one degree of freedom; extensions of the Mantel-Haenszel procedure. J Am Stat Assoc 1963;58:690–700.
16. Minton JP, Abou-Issa H, Reiches N, et al. Clinical and biochemical studies on methylxanthine-related fibrocystic disease. Surgery 1981;90:299–304.
17. Boynton AL, Whitfield JF (eds). The role of cyclic AMP in cell proliferation: a critical assessment of the evidence. Adv Cyclic Nucleotide Res 1983;15:193–294.
18. Barber R, Goka TJ, Butcher RW. Hormone and methylxanthine action on breast epithelial cells. Life Sci 1984;34:2467–76.
19. Curatolo PW, Robertson D. The health consequences of caffeine. Ann Intern Med 1983;98:641–53.
20. Rosenberg L, Slone D, Shapiro S, et al. Case-control studies on the acute effects of coffee upon the risk of myocardial infarction: problems in the selection of a hospital control series. Am J Epidemiol 1981;113:646–52.
21. Silverman DT, Hoover RN, Swanson GM, et al. The prevalence of coffee drinking among hospitalized and population-based control groups. JAMA 1983;249:1877–80.
22. Heyden S. Coffee and fibrocystic breast disease. Surgery 1980;88:741–2.
23. Cole P, Elwood JM, Kaplan SD. Incidence rates and risk factors of benign breast neoplasms. Am J Epidemiol 1978;108:112–20.
24. Marshall JR, Priore R, Graham S, et al. On the distortion of risk estimates in multiple exposure level case-control studies. Am J Epidemiol 1981;113:464–73.